Translation

PATENT COOPERATION TREATY

PCT/FR2003/002382

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FLAMEL0074QT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR2003/002382	International filing date (*day/month/year*) 28 juillet 2003 (28.07.2003)	Priority date (*day/month/year*) 26 juillet 2002 (26.07.2002)
International Patent Classification (IPC) or national classification and IPC A61K 9/50		
Applicant FLAMEL TECHNOLOGIES		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 23 février 2004 (23.02.2004)	Date of completion of this report 20 December 2004 (20.12.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

rnational application No.
PCT/FR2003/002382

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:

pages 1-17, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 1-14, filed with the letter of 17 November 2004 (17.11.2004)

☒ the drawings:

pages 1/2-2/2, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☒ the claims, Nos. 15
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR 03/02382

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-14	YES
	Claims		NO
Inventive step (IS)	Claims	1-14	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-14	YES
	Claims		NO

2. Citations and explanations

1. Reference is made to the following documents:

D1: EP-A-0 709 087 (FLAMEL) 1 May 1996 (1996-05-01)

D2: US-A-5 286 497 (D.L. HENDRICKSON ET AL.) 15 February 1994 (1994-02-15)

D3: US-A-4 894 240 (E.J. GEOGHEGAN ET AL.) 16 January 1990 (1990-01-16)

D4: US-A-5 084 278 (A.M. MEHTA) 28 January 1992 (1992-01-28)

D5: CA-A-2 068 366 (FAULDING) 11 November 1992 (1992-11-11)

D6: WO 02/39984 A (FLAMEL) 23 May 2002 (2002-05-23)

The present application relates to reservoir-type microcapsules coated with a coating film enabling the sustained and controlled release of an active principle that has low solubility in an aqueous medium. The technical problem addressed by the present application is the extremely slow diffusion of active principles of limited solubility through the coating film. The very slow diffusion arises from the low concentration at saturation of the active principle inside the microcapsule. Consequently, to ensure a certain diffusion of the active agent, the coating film must be thin. However, the deposit

of a very thin coating film is not uniform and controlling a thin film deposition method is troublesome and difficult to reproduce under industrial conditions.

The solution proposed in the present application is defined in the subject matter of claim 1. It relates in particular to microcapsules, each of which consists of a core containing an active agent and a specific coating film, characterised in that the core includes an agent for increasing the solubility of the active principle, said solubilizing agent imparting dissolving properties, as defined in said claim, to the core. The addition of the solubilizing agent consequently enables a coating film to be deposited that is sufficiently thick to be industrially reproducible.

The subject matter of the present claim 1 is considered novel (PCT Article 33(2)), given that none of the documents cited in the international search report discloses microcapsules as defined in claim 1. The subject matter of the claim also involves an inventive step (PCT Article 33(3)), in so far as it is not rendered obvious by reading the cited documents. In particular, the cited prior art contains no indications that would prompt a person skilled in the art to develop microcapsules such as those defined in claim 1. Furthermore, none of the cited documents addresses the problem of diffusing active principles of low solubility towards the outside of a microcapsule.

D1 (cf. examples 4 and 6) discloses reservoir-type microcapsules containing an active principle of low solubility, in particular aciclovir and cimetidine. The core of said microcapsules consists of a mixture of the active principle and a small amount of

polyvinylpyrrolidone as a binder. The core is coated with a film including an insoluble polymer, a soluble polymer and a plasticizer. However, D1 does not disclose the addition to the core of a solubilizing agent imparting dissolving properties, as defined in claim 1, thereto. The presence of a very small amount of polyvinylpyrrolidone as a binder does not, in principle, lead to a microcapsule as claimed in the present application. Furthermore, on reading D1, a person skilled in the art would find no indication that would prompt him or her to add a solubilizing agent as claimed, with a view to increasing the solubility, and hence the diffusion, of an active agent of low solubility through the coating film. In particular, the problem addressed in D1 concerns providing microcapsules designed to transit through the small intestine slowly, i.e. more slowly than natural transit.

In a similar manner to D1, D2 and D3 disclose microcapsules enabling the controlled release of an active principle of low solubility, in this instance diltiazem. However, said prior art documents do not disclose the addition to the core of a solubilizing agent imparting dissolving properties, as defined in claim 1, to the core containing the active principle of low solubility. In this instance also, the presence of a very small amount of polyvinylpyrrolidone and/or carboxymethylcellulose as a binder does not, in principle, lead to a microcapsule as claimed in the present application. Furthermore, D2 and D3 do not address the problem of achieving very slow diffusion of an active principle of low solubility through a coating film. Said documents relate to providing a formulation that releases the diltiazem in a sustained and gradual manner over a period of 24 hours, thereby limiting the number of administrations.

D4 relates to a coating film enabling the taste of the active principle to be masked. D5 relates to a coating film suitable for use in a spray-drying method. None of the documents suggests adding a solubilizing agent to microcapsules containing an active principle of low solubility. D6 relates to microcapsules containing a highly soluble active principle.

Claims 2 to 14 are dependent on claim 1 and thus also comply, as such, with the PCT requirements of novelty and inventive step.

The subject matter of claims 1 to 14 is industrially applicable and consequently meets the requirements of PCT Article 33(4).